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Sotos Syndrome: Evolution of Facial Phenotype Subjective and Objective Assessment

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Sotos syndrome is characterised by pre- and post-natal growth acceleration, advanced bone age, developmental delay and a typical facial Gestalt. We have evaluated 45 individuals with Sotos syndrome who were between age 1 and 25 years, in order to better define the change in facial appearance over time. In each individual, a thorough assessment was made, serial photographs were reviewed, and a series of anthropometric craniofacial measurements was obtained. These were compared with age- and sex-matched normal standards.

Both clinical and anthropometric evaluations show that the facial appearance which most clinical geneticists would regard as "classical" is established early in life. The head is large and dolichocephalic, with a rounded and prominent forehead, accentuated by frontoparietal balding. There is narrowing at the temples, fullness of the cheeks, and tapering to a pointed chin. With time, the normal process of facial change occurs, superimposed on that typical Gestalt. As the face lengthens, the dominance of the forehead diminishes and the chin achieves greater prominence. The mandible is long and narrow inferiorly, square or pointed, but prognathism is rare. In a small proportion of patients, a rounder face early in life may challenge diagnosis, but follow-up of these large newborn and older infants should allow diagnosis by early childhood.

Visualisation of pattern profiles at different ages, supplemented by statistical measures of variability and similarity, support the clinical impressions outlined above.

KEY WORDS: Sotos syndrome, facial phenotype, craniofacial pattern profiles, anthropometry

INTRODUCTION

Age-related changes in facial phenotype are now well-recognised [Allanson, 1989], and are increasingly incorporated into syndrome delineation [Allanson et al., 1985; Allanson, 1988, 1990; Porteous and Goudie, 1991; Lopez-Rangel et al., 1992; Hughes-Benzie et al., 1992; Fryns, 1992; Allanson et al., 1993; Hunter and Allanson, 1994; Stevenson et al., 1995]. Objective evaluation of the face, through the use of anthropometry, cephalometry, or photogrammetry, has been used to supplement syndrome identification for many years [reviewed in Meaney and Farrer, 1986; Allanson, this issue]. Anthropometry can enhance subjective or Gestalt impressions of facial appearance, particularly if individual measurements are converted into Z scores, to produce a pattern profile [Garn et al., 1984]. Any dimension characterised by a high or low Z score is immediately obvious and serves to identify craniofacial areas that are most unusual or characteristic of a particular syndrome. Pattern profiles can be applied across age groups and may demonstrate persistence or change in facial appearance with time. They also allow comparison between a single individual and a group with a known diagnosis. To supplement a simple visual appreciation of these pattern profiles, statistical measures of similarity and variability can be calculated. The correlation coefficient, r_z, is computed from paired Z scores of two pattern profiles to provide a numerical indication of the similarity of any two patterns. The pattern variability index, σ_z, expresses the degree of dysmorphogenesis as a single number. The more highly patterned an individual, the greater the deviation from the reference population, and the greater the variability index.

Syndrome-specific patterns have been compiled in Wiedemann-Beckwith syndrome [Ward et al., 1990; Hunter and Allanson, 1994], Simpson-Golabi-Behmel syndrome [Hughes-Benzie et al., 1992], hypohidrotic ectodermal dysplasia [Ward and Bixler, 1987], Down

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syndrome [Allanson et al., 1993], and Williams syndrome (Pober, personal communication). These may be used not only for diagnosis of affected individuals but also to assist the identification of carriers [Ward and Bixler, 1987; Hughes-Benzie et al., 1992].

Sotos syndrome (SS) is characterised by pre- and postnatal growth acceleration, advanced bone age, and developmental delay. The typical face of SS is well established, striking, and poses little diagnostic difficulty. The aim of our study was to determine whether the early facial appearance was similar, whether significant change occurred with age, and whether the gestalt became less obvious in adulthood, as some have suggested [Cole and Hughes, 1990]. To that end, we evaluated 45 individuals with SS between the age of one and 25 years.

MATERIALS AND METHODS

Forty-five Caucasian individuals with SS, age 1 to 25 years, were ascertained. Most were referred to one of the authors (TRPC). The diagnostic criteria for SS and method of exclusion of alternative diagnoses, such as fragile X, in this group is reviewed in Cole and Hughes [1994]. In all remaining subjects, Fragile X syndrome was ruled out by molecular testing. A series of anthropometric measurements was obtained on each subject (Table I) following the method published by Farkas [1981]. Measurements were recorded to the nearest 0.5 millimeter using GPM sliding and spreading, blunt-ended calipers, and a paper metric tape measure. These dimensions were chosen to represent craniofacial widths, lengths, depths, heights, and circumferences plus details of ear, eye, nose, and mouth structure (Fig. 1). For each dimension, age- and sex-matched normal standards were available. The population norms were derived from measurements of the head and face in 2,326 healthy North American Caucasian children and young adults [Farkas, 1994]. Measurements were taken by one of the authors (JEA). The raw data were compared to normal standards and converted to Z scores to control for age and sex differences. Pattern profiles were compiled for each age and sex. Because of small numbers at certain ages, additional profiles were produced for chosen groups of subjects: ages 6, 9, 12, 17, and adult. Correlation coefficients and variability indices were generated by the Statistical Package for Social Scientists (SPSS), using the methods published by Garn [Garn et al., 1984, 1985].

RESULTS

Subjective Craniofacial Assessment

The head is large at birth, and remains large and dolichocephalic throughout life. The classical facial shape may be present at the outset (Fig. 2). It is an "inverted pear," tapering from the broad forehead to a small chin, with narrowness at the skull base and temples. The forehead is rounded and prominent, this appearance being accentuated by frontoparietal balding. The ears, nose, and mouth are unremarkable; the philtrum is fairly well grooved, and the chin is small. The eyes appear wide-spaced secondary to narrowness at the temples, but true hypertelorism is not found.

Although the classical facial shape may be obvious from the neonatal period, a few infants display a rounder facial appearance with a flatter profile and fleshier cheeks. However, even in this latter group, the more typical shape develops within the first 1 to 2 years (Fig. 3a,b).

The toddler almost invariably demonstrates the typical face of SS, with its "inverted pear" shape and persistent marked frontoparietal balding (Fig. 3b). In some cases, the face may appear quite gaunt. Apparent hypertelorism persists and lateral supraorbital fullness simulates a down-slant to the palpe-

TABLE I. Anthropometric Measurements Employed in This Study

Head width	eu-eu	eurion to eurion
Skull base width	t-t	tragion to tragion
Minimum frontal width	mf-mf	frontotemporale to frontotemporale
Upper facial width	zy-zy	zygion to zygion
Lower facial width	go-go	gonion to gonion
Head length	g-op	glabella to opisthocranion
Upper facial depth	t-n	tragion to nasion
Midfacial depth	t-sn	tragion to subnasale
Lower facial depth	t-gn	tragion to gnathion
Nasal protrusion	sn-prn	subnasale to pronasale
Total facial height	n-gn	nasion to gnathion
Upper facial height	n-sn	nasion to subnasale
Nasal width	al-al	alare to alare
Mouth width	ch-ch	cheilion to cheilion
Inner canthal distance	en-en	endocanthion to endocanthion
Outer canthal distance	ex-ex	exocanthion to exocanthion
Ear width	pra-pa	preaurale to postaurale
Ear length	sa-sba	superaurale to subaurale
Maxillary arc	t-sn-t	tragion to subnasale to tragion
Mandibular arc	t-gn-t	tragion to gnathion to tragion
Head circumference	OFC	maximum circumference in horizontal plane at level of glabella and opisthocranion

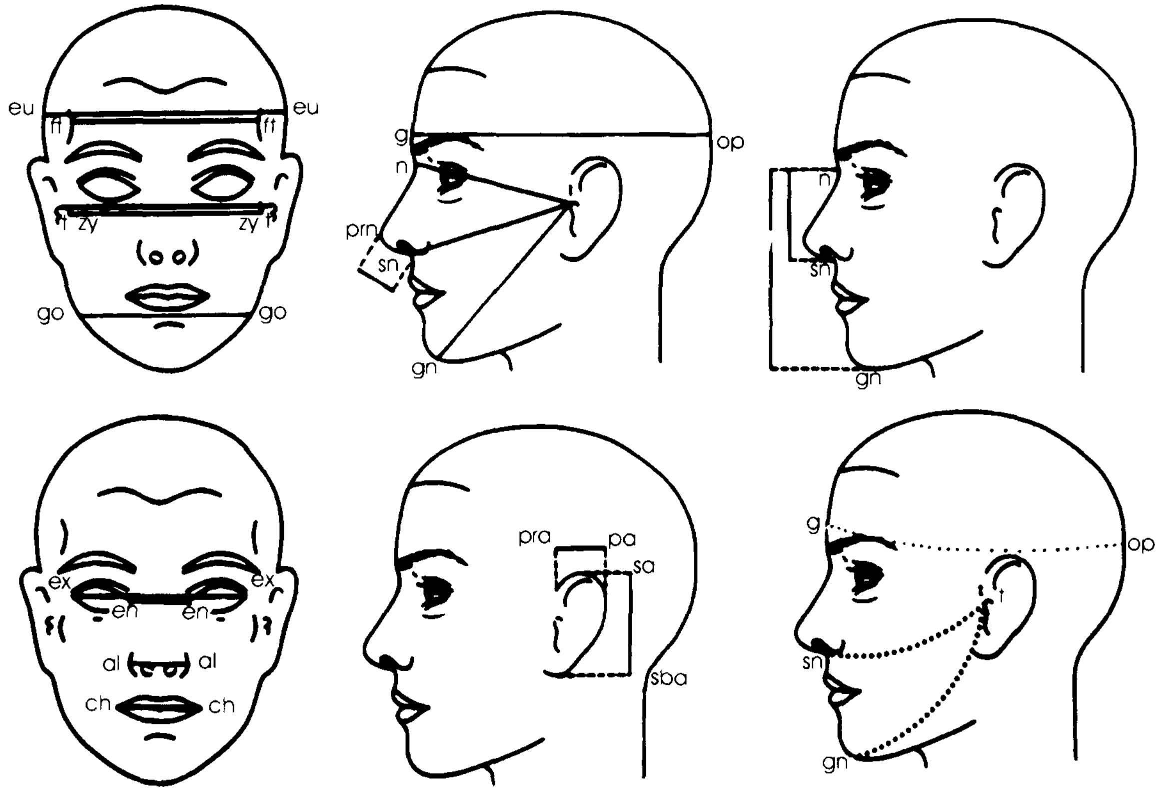

Fig. 1. Anthropometric dimensions employed in this study. Figure adapted, with permission, from "Anthropometric Facial Proportions in Medicine," Farkas LG and Munro IR, Charles C Thomas, Springfield, Illinois, 1987.

Fig. 2. The face of infancy.

bral fissures. Strabismus is fairly common. The nose tends to have a prominent root with a low, scooped bridge and "skijump" tip. Lengthening of the chin contributes most to the impression of elongation of the face.

In the young child the overall Gestalt changes little. The dominance of forehead over face remains striking; gauntness may persist. Palpebral fissures may be truly downslanting or that appearance may be secondary to lateral supraorbital fullness. The chin is long but not protruding. There is frequently a rosy colouration of the nasal tip and cheeks.

With increasing age, the chin becomes more striking, tending to be narrow and relatively pointed (Fig. 4). It is rarely prognathic. The "skijump" nasal profile remains common, with anteverted nares, although lengthening of the tip may be seen. Hair growth in the frontoparietal region is still sparse.

In the young adult, these facial proportions are maintained (Fig. 5). The mandible is long and narrow inferiorly, square, or pointed. Prognathism is rare. Eyebrows are prominent, thick and may extend further laterally than usual. At this age, the Gestalt may be quite subtle.

Anthropometric Craniofacial Assessment

Pattern profiles have been compiled at five ages where there were three or more patient data sets, since

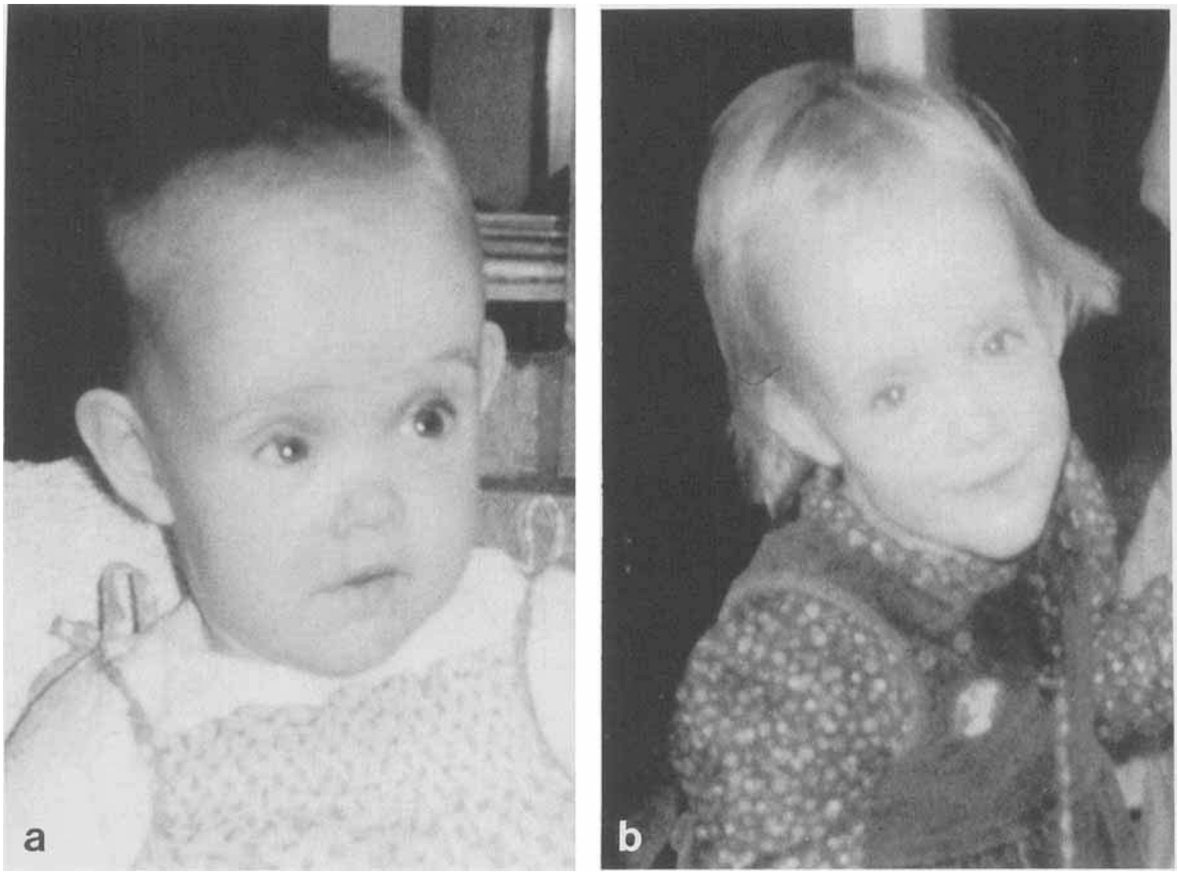

Fig. 3. **a**: Facial appearance in a proportion of infants, demonstrating a rounder shape, with less evidence of the typical "inverted pear". **b**: The same child at age 3 when facial shape has assumed a more characteristic shape.

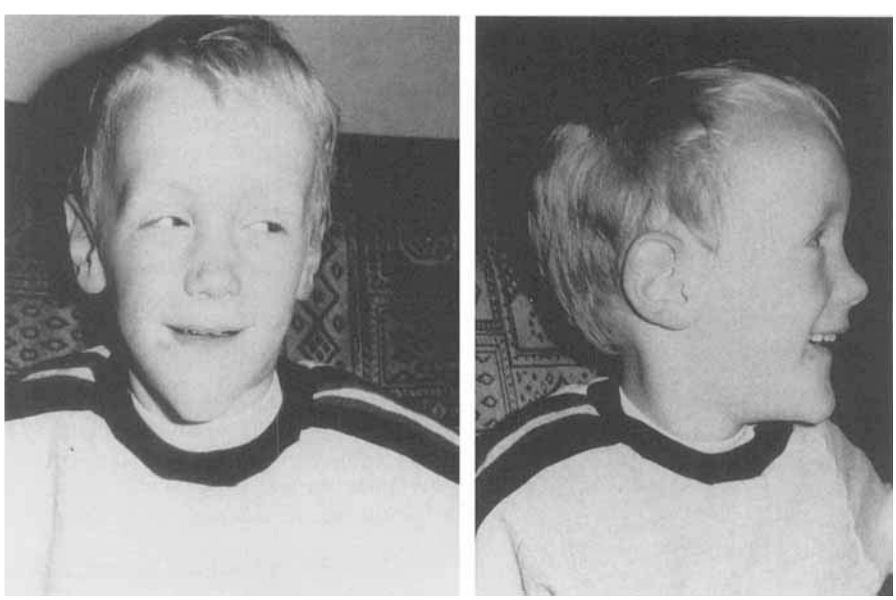

Fig. 4. The face in middle childhood.

Fig. 5. The young adult with Sotos syndrome.

single cases often are not representative and may be misleading (Fig. 6). From age 6 to adulthood there is some pattern consistency, particularly in facial widths, depths, and heights. Head circumference (ofc), width (eu-eu), and length (g-op) are increased as expected; head length deviates from normal to a greater extent than width, confirming dolichocephaly. Mandibular dimensions (width: go-go; depth: t-gn; circumference: t-gn-t) are almost always greater than the maxillary counterparts (zy-zy, t-sn and t-sn-t, respectively), and are further away from the norm, emphasising an excess in mandibular growth in comparison to maxillary growth.

The pattern consistency seen at different ages in SS suggests that the normal facial changes which occur with age in any individual are superimposed on the pattern which is characteristic of this condition. That typical pattern is established early.

If the profile in the 1-year-old child is now compared to the original five age group profiles (Fig. 7), certain differences are noteworthy. Bizygomatic diameter (upper facial width) is greater than bigonial (lower facial width); maxillary depth (t-sn) and circumference (t-sn-t) are larger than their mandibular counterparts (t-gn and t-gn-t). This validates the impression of a rounder face in early life, with mandibular dominance being a later phenomenon.

Statistical Analysis

The Pattern Variability Index, σ_z was calculated for the 1-year-old, and the groups at age 6, 9, 12, 17, and adult. Results are listed in Table II. All values are close to, or exceed 1.2, the value which denotes the upper limit of patterned variation in the general population [Garn et al., 1985]. Correlation coefficients, r_z, were calculated for all possible pairs of age groups. The results are described in Table III accompanied by two-tailed significance values. This analysis documents the poor correlation between age 1 and older age groups, where the maximum pattern similarity (r_z) is 0.42. By comparison, when the other five age groups are evaluated, minimum pattern similarity is 0.58 (age 6 group and adult group), and maximum pattern similarity is 0.85 (age 9 group and age 12 group): a significantly high correlation. This analysis supports the initial interpretation derived from visualisation of the pattern profiles, which suggests pattern consistency at age 6 and above, with reduced similarity when age 1 is compared to all older groups.

DISCUSSION

This study of individuals with SS compliments and augments our knowledge of facial appearance in this condition. Attention is drawn to the early establishment of the "classical" phenotype. Clinical and anthropometric analysis show that the head is large at birth, and remains large and dolichocephalic, with a prominent forehead, throughout life. The face is initially round, but quickly attains a more typical oval shape, with narrowness at the skull base and in the bizygomatic area, producing an "inverted pear" shape. This leads to the impression of hypertelorism, which is not substantiated by anthropometry. In childhood, the face often appears gaunt, with little subcutaneous tissue. With age, mandibular growth is striking but prognathism is unusual; the forehead remains broad and prominent; palpebral fissures are down-slanting with lateral supraorbital fullness. The adult face maintains characteristic proportions; however the Gestalt is less striking, making diagnosis more difficult, particularly as height in the adult may not exceed the normal range.

Beyond simple visual comparisons, however valuable, there are numerical measures of clinical value. The pattern variability index provides an indication of the extent to which an individual or group of individuals deviates from the reference population. The higher the index, the more aberrant the appearance of the individual or group. This is a useful quantitative

TABLE II. Pattern Variability Indices

Age/age group	σ_z
Age 1	1.37
Age 6 group	1.18
Age 9 group	1.36
Age 12 group	1.16
Age 17 group	1.36
Adult group	1.41

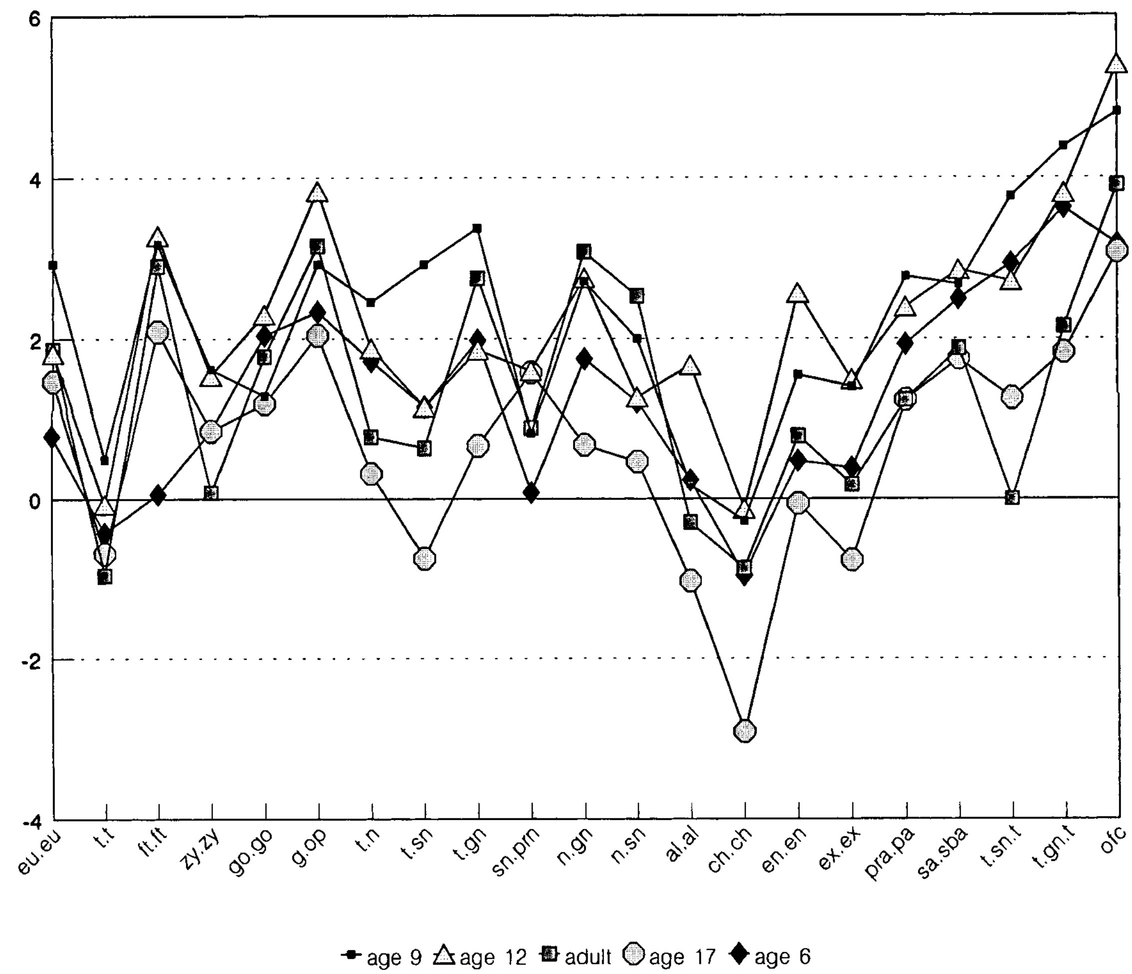

Fig. 6. Craniofacial pattern profiles in five age groups, from middle childhood to adulthood.

measure of the degree of dysmorphogenesis. When applied to standardised cephalometric measurements of the head and face, a σ_z of 1.2 approximates the 95th percentile of the normal range of children and adults [Garn et al., 1985]. If the same judgement can be made of anthropometric measurements, all subjects in this study demonstrate variability at or beyond the expected range. The measure of pattern profile similarity, r_z, allows one to compare individuals or groups. This study demonstrates significant similarity between age groups 6 and above, with the 1 year old having less in common.

The age-related changes in SS are similar to those found in the general population, with lengthening of the face, loss of initial forehead dominance, and subsequent mandibular dominance [Allanson, 1989]. However, these are superimposed on the pre-existing SS pattern. In essence, the typical face is seen at any age, and can be recognised as such. In a small proportion of patients, a rounder face in infancy may challenge diagnosis, but follow-up of these individuals should allow accurate diagnosis by early childhood.

This fairly consistent facial pattern over time contrasts with the situation in several other syndromes, and might not have been anticipated. In Noonan and Wiedemann-Beckwith syndromes, facial phenotype becomes less characteristic with time, to the extent that the adult face may show few, if any, abnormalities [Allanson et al., 1985; Hunter and Allanson, 1994]. The opposite is true in Rubinstein-Taybi syndrome, where the facial Gestalt is quite unremarkable in the neonate and infant, and typical features only begin to emerge in middle childhood [Allanson, 1990].

CONCLUSION

Sotos syndrome is a fairly uncommon overgrowth syndrome, with a typical facial phenotype that should be recognised early. The appearance remains relatively unchanged, except for superimposition of the usual age-related changes of shape and proportion. A craniofacial pattern profile has been compiled which emphasises macrodolichocephaly, with mandibular dimensions consistently in excess of maxillary counterparts. Visualisation of pattern profiles reveals a marked sim-

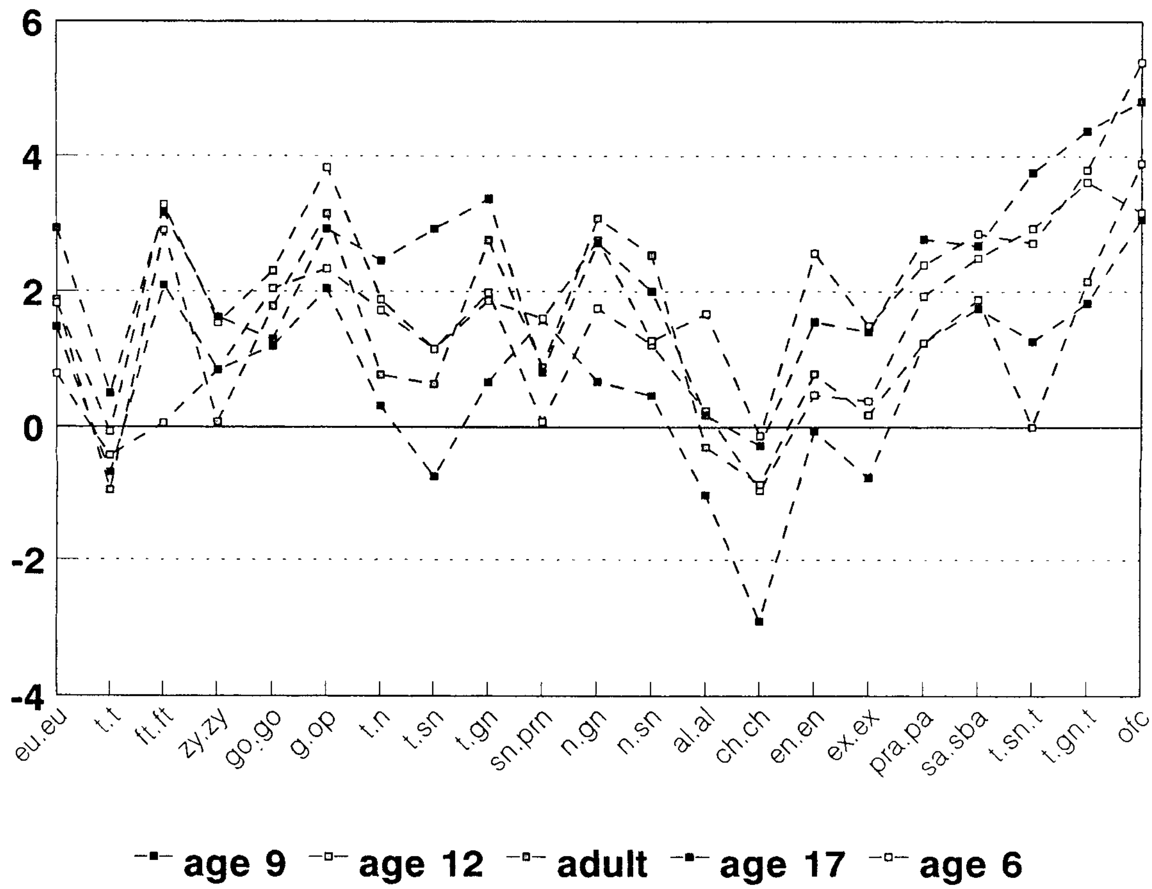

Fig. 7. Pattern profile of original five groups, with the addition of a single profile in infancy which shows some discrepant features.

ilarity among age groups 6 years and above, with some differences in the young child. Statistical estimates of variability and similarity, σ_z and r_z, support this conclusion.

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TABLE III. Correlation Coefficients

	Age 1	Age 6 group	Age 9 group	Age 12 group	Age 17 group	Adult group
Age 1	1.000	.1948	.2566	.3103	.4175	.2279
Age 6 group	.1948	1.000	.7576*	.7029*	.6387	.5726
Age 9 group	.2566	.7576*	1.000	.8525*	.7061*	.5913
Age 12 group	.3103	.7029*	.8525*	1.000	.7427*	.7036*
Age 17 group	.4175	.6387	.7061*	.7427*	1.000	.5897
Adult group	.2279	.5726	.5913	.7036*	.5897	1.000

*Denotes two-tailed significance $P < .001$.

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